Computational modelling for predictive tissue engineering

Hans Van Oosterwyck[1,2]

[1]*Department of Mechanical Engineering (Biomechanics section), KU Leuven, Belgium, hans.vanoosterwyck@kuleuven.be*

[2]*Prometheus, Division of Skeletal Tissue Enginering, KU Leuven, Belgium*

The success of cell-based tissue engineering strategies relies on controlling cell fate, meaning among others that depending on the application or process of interest, one wants to control cell recruitment, proliferation and/or differentiation in a spatially and temporally orchestrated way. This spatial and temporal organisation of multicellular behaviour are crucial aspects of tissue development, where cell collective behaviour emerges from single cell behaviour, which relies on the execution of complex (intracellular) signaling programs. In turn these programs are steered by extracellular signals, which can be of chemical or physical origin on the one hand, and related to cell-cell or cell-matrix interactions on the other hand. In this presention, examples are shown how computational models can help in quantifying extracellular signals and how these signals affect multicellular organisation and tissue formation.

A first example will focus on bone regeneration, and how the complex interplay of oxygen, growth factors and cells in relation to host environmental conditions can explain the occurrence of bone fracture non-unions. To this purpose a multiscale, computational model was built that combined agent-based modelling of angiogenesis to a continuum-type model of bone formation. The model was among others used to explore the outcome of the local injection of osteochondroprogenitor cells, growth factors or the combination therefore in critical sized segmental defects (figure 1). Interestingly the model predicted an optimal healing response when cellular injections (either or not in combination with growth factors) were delayed until two to three weeks after fracture initiation. For growth factor injection only no positive effect was seen.

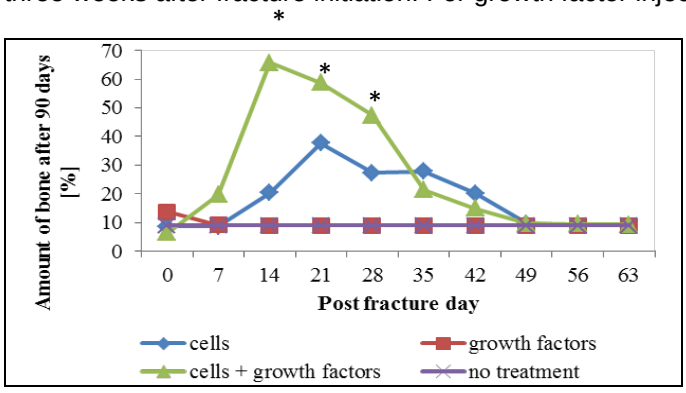

Figure 1: Predicted amount of bone formed at PFD (post fracture day) 90 as a function of the PFD at which the treatments, consisting of a single injection of cells, growth factors or a combination thereof, was initiated. The conditions indicated with * resulted in a complete healing of the large segmental defect.

A second example focuses on the use of cell mechanical models to explain self-aggregation in microwells. These aggregates can be used as model systems of tissue organisation, or when assembled in larger structures can be part of a tissue engineering therapy. Meshless, particle-based modelling techniques were used to capture quantitative aspects of single cell mechanical behaviour (such as viscoelasticity of the cell cortex), cell-cell and cell-substrate mechanical interactions. Chemotaxis-mediated migration was implemented as well. It was found that aggregation can be described as a function of cell-substrate adhesion, contractility and cell motility. Furthermore, as the models provide quantitative information on cell stresses, this information can in a later stage be linked to cell fate changes.

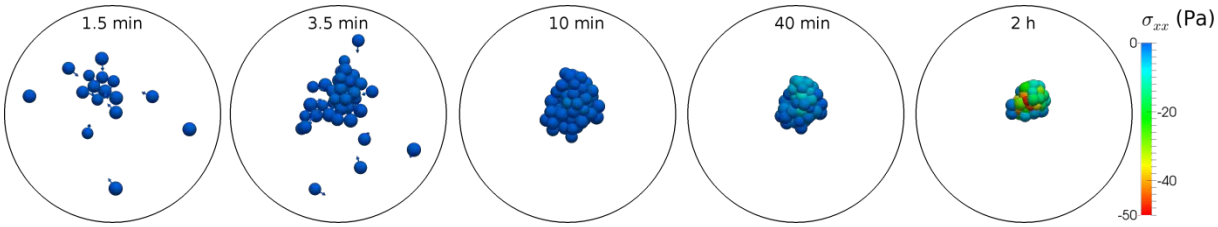

Figure 2: Particle-based simulation of the formation of aggregates in micro-wells. Cells have aggregated after 10 minutes and then condensate. After 2 hours an almost spherical aggregate is found. Cells are colour-coded for compressive principal stress (in Pa), arrows indicate migration direction (only visible during aggregation phase).

These examples illustrate how computational models can be used to approach tissue engineering systems and strategies in a more quantitative and predictive way, and to study behaviour that emerges for complex biological interactions (as in the case of fracture healing) or mechanical interactions (as in the case of micro-aggregation). By more systematically running such simulations parallel to and in combination with experiments to look for governing mechanisms, it is foreseen that computational models can help in reducing the amount of trial-and-error, thereby leading to a more effective way of developing new or better strategies.

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